TREATMENT OF PERIODONTITIS

The present invention relates to the prevention, inhibition and/or reduction of periodontitis by the use of a medicament that comprises Triclosan (=2',4,4'-trichloro-2-hydroxy-diphenyl-ether).

Periodontitis is a general term describing specific diseases affecting the gingiva and the supporting connective tissue and alveolar bone which anchor the teeth in the jaws. Periodontitis causes loss of connective tissue, resorption of alveolar bone and formation of periodontal pockets, and may lead to a loosening of the teeth, and ultimately to the loss of teeth.

Periodontal disease is mainly caused by specific anaerobic bacteria in the periodontal pockets. The destruction of the periodontal tissue is primarily caused by the indirect effects mediated by the host's reaction to the bacteria. Bacterial metabolites induce leucocyte chemotaxis which results in the inflammatory cells accumulating at the site of the bacterial challenge. Furthermore, bacterial metabolites induce the production of inflammatory mediators by leucocytic cells, in particular monocytes. Amongst these are local disease mediators such as metabolites of arachidonic acid, e.g. leukotrienes, prostaglandins and thromboxanes. Additionally, the loss of alveolar bone may be directly induced by pathogenic metabolites of bacteria, in particular proteolyte enzymes. Prostaglandins have been found to be particularly important in the metabolism and destruction of tissue and alveolar bone. Indeed, the production of prostaglandins in the periodontal tissues has been found to be an important mediator of the loss of alveolar bone in the periodontium; patients with periodontal breakdown show an elevated prostaglandin E_2 level both in the gingival tissue as well as in the crevicular fluid. Prostaglandins and thromboxanes are formed from arachidonic acid by an enzyme cascade, the first step of which is the cyclo-oxygenation by an enzyme called cyclo-oxygenase. Inhibiting the cyclo-oxygenase would inhibit the formation of prostaglandins and thus reduce alveolar bone loss, and indeed certain cyclo-oxygenase inhibitors, particularly non steroidal anti-inflammatory drugs such as indomethacin and flurbiprofen have been found to markedly reduce the resorption of alveolar bone.

We have now found that Triclosan has a considerable anti-cyclo-oxygenase activity, thus significantly inhibiting the formation of prostaglandins. Inhibiting the biosynthesis of the prostaglandins locally would thereby significantly inhibit or prevent alveolar bone resorption. Triclosan has been shown to be retained by gingival tissue both in vitro and in vivo following topical application.

In this respect, it is observed that in the prior art it has been suggested to treat periodontal diseases with a combination of a non steroidal anti-inflammatory drug and an antimicrobial agent, e.g. the combination of aspirin, indomethacin or phenylbutazone with an antibacterial quaternary ammonium compound, such as cetylpyridinium chloride or a bis-biguanide compound such as chlorhexidine digluconate (GB 1,489,672).

Similar combinations are disclosed in GB 1,550,139, wherein the non steroidal anti-inflammatory agent can be selected from various classes of such agents, including indomethacin, ibuprofen, diclofenac and so on.

In U.S. Pat. No. 4,742,083 it has been disclosed that certain substituted salicylamides demonstrate an anti-inflammatory and an antimicrobial action. These salicylamides have previously been proposed for inclusion in oral compositions as anti-plaque agents (U.S. Pat. No. 4,287,191 and U.S. Pat. No. 4,358,443). However, Triclosan has been found to be a much more potent anti-inflammatory agent than the preferred substituted salicylamides of these references (which are also stated to be prostaglandin synthetase inhibitors).

Consequently, the present invention relates to the use of Triclosan in the manufacture of a medicament for inhibiting prostaglandin-forming cyclo-oxygenase activity. More particularly, it relates to the use of Triclosan in the manufacture of a medicament for preventing or inhibiting alveolar bone resorption. It relates especially to the use of Triclosan as prostaglandin-forming cyclo-oxygenase inhibitor in the manufacture of a medicament for preventing or reducing periodontitis.

Triclosan is a well-known anti-bacterial agent, used i.a. in oral compositions to reduce or inhibit the growth of dental plaque. Its use to inhibit cyclo-oxygenase activity to prevent or inhibit alveolar bone resorption or periodontitis has not been indicated in the prior art as far as we know.

Since Triclosan also has anti-bacterial activity, it not only modulates the host response system by inhibiting cyclo-oxygenase activity, but also reduces the microbial challenge, thus having a highly desirable combined, dual effect to prevent or reduce periodontitis.

The Triclosan-containing medicament of the present invention can be manufactured in any form, suitable for administering the medicament to achieve the reduction or prevention of periodontitis. Such forms are tablets, capsules, pills, powders, granules, solutions, suspensions, salves, gels, pastes etc. Suitable forms for oral administration are toothpastes, mouthwashes, gels and the like. Also it is possible to formulate the medicament in forms, suitable for topical and buccal administration, e.g. for dosing in the pockets by special applications, such as irrigator fluids, flosses, chewing gum, lozenges, fibres (hollow and monolytic), adhesive strips, tooth picks and the like.

The amount of Triclosan used in the present invention may vary from 0.0001–5, preferably 1% by weight of the medicament.

The Triclosan is preferably used in an amount above its MIC-values for certain micro organisms occurring in the pockets, known to contribute to periodontitis such as strains from the genera Actinomyces, Bacteroides, Peptococcus, Peptostreptococeus, Veillonella, Actinobacillus, Eubacteria, Fusobacteria and Liptotrichia, e.g. *Bacteroides gingivalis, B. intermedius, Actinobacillus actinomycetemcomitans.* The MIC-value of Triclosan for the latter is 0.0005%, and for all the other species between 0.001 and 0.005%.

The medicament furthermore may comprise further, conventional ingredients, such as pharmaceutically acceptable carriers like starch, sucrose, polyols, surfactants, water or water/alcohol systems etc. When formulated into a dentifrice, such formulation may contain all the usual dentifrice ingredients. Thus, they may comprise particulate abrasive materials such as silicas, aluminas, calcium carbonates, dicalciumphosphates, hydroxyapatites, trimetaphosphates, insoluble hexametaphosphates and so on, usually in amounts between 5 and 60% by weight.

Furthermore, they may comprise humectants such as glycerol, sorbitol, propyleneglycol, lactitol and so on.